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Arsenic Exposure and Glucose Metabolism: Experimental Studies Suggest Implications for Type 2 Diabetes

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Epidemiological studies from around the globe have turned up associations between exposure to arsenic and type 2 diabetes.[1,2,3] A state-of-the-science review by researchers at the University of California (UC) Berkeley and UC Davis, published recently in *Environmental Health Perspectives*, assesses relevant experimental work to elucidate arsenic's disruptive effects on glucose homeostasis, a key step in diabetogenesis.[4] Understanding the cellular mechanisms that underlie the epidemiological data can help prove the biological plausibility of the link between arsenic and diabetes and inform public health practices, says review coauthor Michele La Merrill, a toxicologist at UC Davis.

An expert panel assembled by the National Toxicology Program in 2011 found animal research on the topic of arsenic and diabetes to be inconclusive, due largely to dissimilarities between animal exposures across studies and those reported in human exposure studies.[5] Yet, in the past decade, a large number of animal and cellular studies have emerged that have been designed to mimic internal arsenic doses observed in humans and the effects of those doses on how cells in the body use glucose.[4]

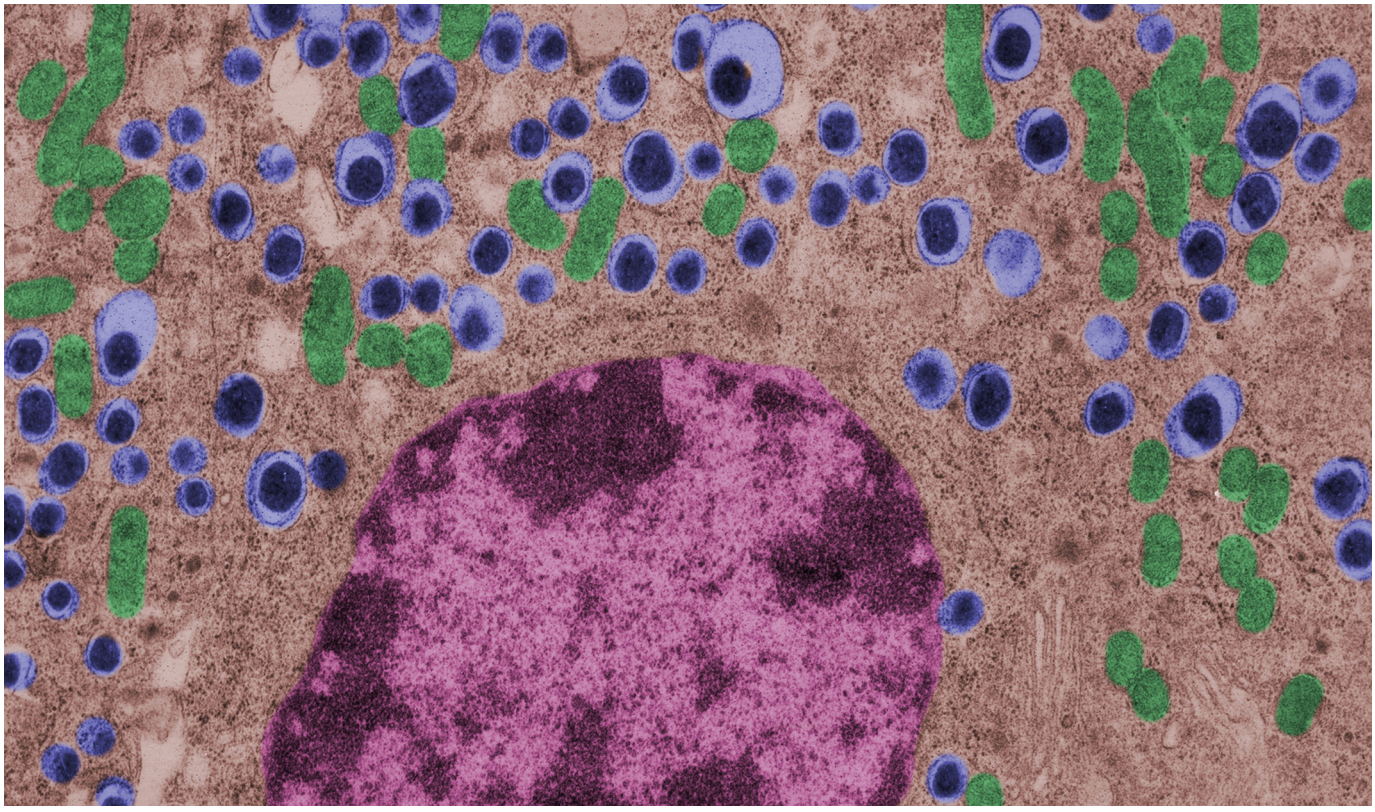
In the present review, researchers including first author Felicia Castriota, then a PhD candidate at UC Berkeley, synthesized the findings of 47 *in vivo* and *in vitro* studies to highlight likely molecular mechanisms by which arsenic may affect diabetes. They focused on an inorganic form of arsenic called arsenite and excluded studies looking only at *in utero* exposures.

The studies assessed several outcomes related to the body's ability to process glucose. For instance, two studies in C57BL/6J mice showed that glucose tolerance—how well cells use glucose after a meal—may be impaired at a high dose (50 ppm) of arsenic, leading to excessive blood glucose levels.[6,7] Yet, at the lowest dose tested for glucose tolerance (3 ppm), this effect was seen only in a mouse model of diabetes.[8]

Arsenic may also target insulin secretion and signaling. "Perturbations in insulin secretion and insulin signaling are both really important for the pathology of diabetes," says La Merrill. Insulin stimulates muscle and fat tissue to take up and store glucose. When the cells in these tissues become resistant to insulin—the key step in the development of type 2 diabetes—an individual's blood glucose rises.[9]

Additionally, arsenite may affect β cells, the cells in the pancreas that produce insulin. At high doses, arsenic increased apoptosis, reducing the number of cells capable of producing insulin. Low-dose exposures inhibited insulin production itself.

The researchers also identified 16 genes that are affected by arsenite, insulin resistance, and type 2 diabetes. "Identifying genes that are commonly related by these three elements can give us new



This micrograph of a pancreatic β cell shows insulin granules in blue, mitochondria in green, and the nucleus in purple. Disruption of β cell function is one of several potential mechanisms that could explain the association between arsenic exposure and type 2 diabetes. Image: © Jose Luis Calvo/Science Source.

targets for future research," says Shohreh Farzan, an assistant professor of preventive medicine at the Keck School of Medicine at the University of Southern California, who was not involved in the review. "We see arsenic acting in multiple ways on glucose metabolism. Follow-up in human populations can give us a sense of what may be the most important pathways or mechanisms contributing to diabetes that may be impacted by arsenic exposure."

A potential limitation of the review, points out Ana Navas-Acien, an epidemiologist at Columbia University, is that it focused on studies of arsenite toxicity. "While some human populations may be exposed to arsenite, it may not be the most relevant species for humans," says Navas-Acien, who was not involved in the review. She says humans are more commonly exposed to arsenate, the arsenic species that dominates oxygenated waters.[10] Few animal studies to date have used arsenate. However, arsenate is rapidly converted to arsenite.[11] She adds that the paper also did not include a comprehensive review of the role that prenatal arsenic exposure may play in diabetes onset.

Navas-Acien says future studies should further investigate the toxicity of methylated arsenic species. Methylation takes place when the body attempts to metabolize arsenic, she explains, and there is some evidence to suggest that this process may increase the toxicity of arsenic in the body.[12] Notably, however, rodents and humans metabolize arsenic differently,[13] which complicates the application of experimental findings to observations in humans.

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